Metabolic Alkalosis: the Missing Puzzle Piece

By
Prof. Ashraf Abdel Basset
Professor of Pediatrics

Case Presentation

History:

- A three-year old previously healthy female presented with recurrent episodes of quadriparesis.

Examination:

- Apparently healthy female.
- Her blood pressure was 90/60.
- Apart from generalized hypotonia, her neurological examination was unremarkable.

Follow Up

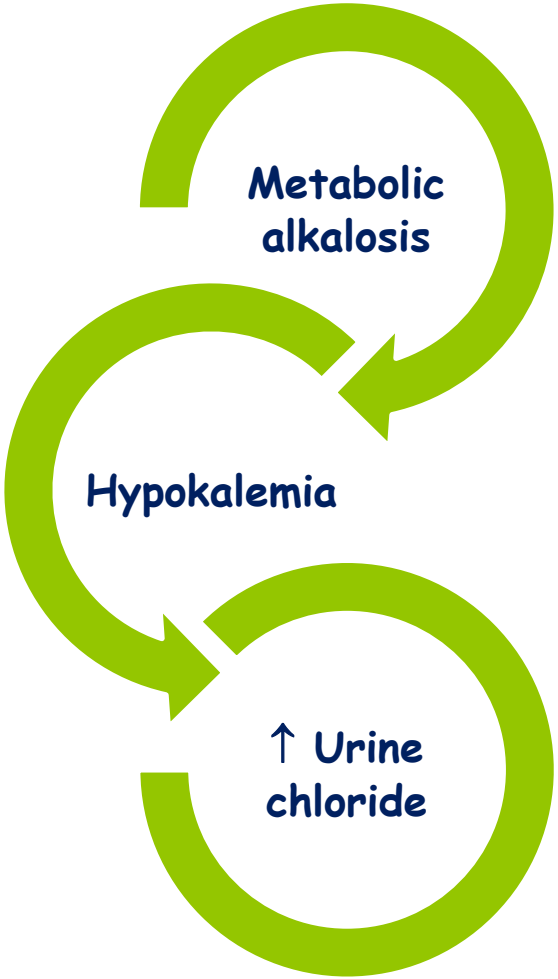
- She was followed in the pediatric neurology outpatient clinic as a case of periodic paralysis.
- Few months later, she developed a similar attack of quadriparesis.

Laboratory Investigations:

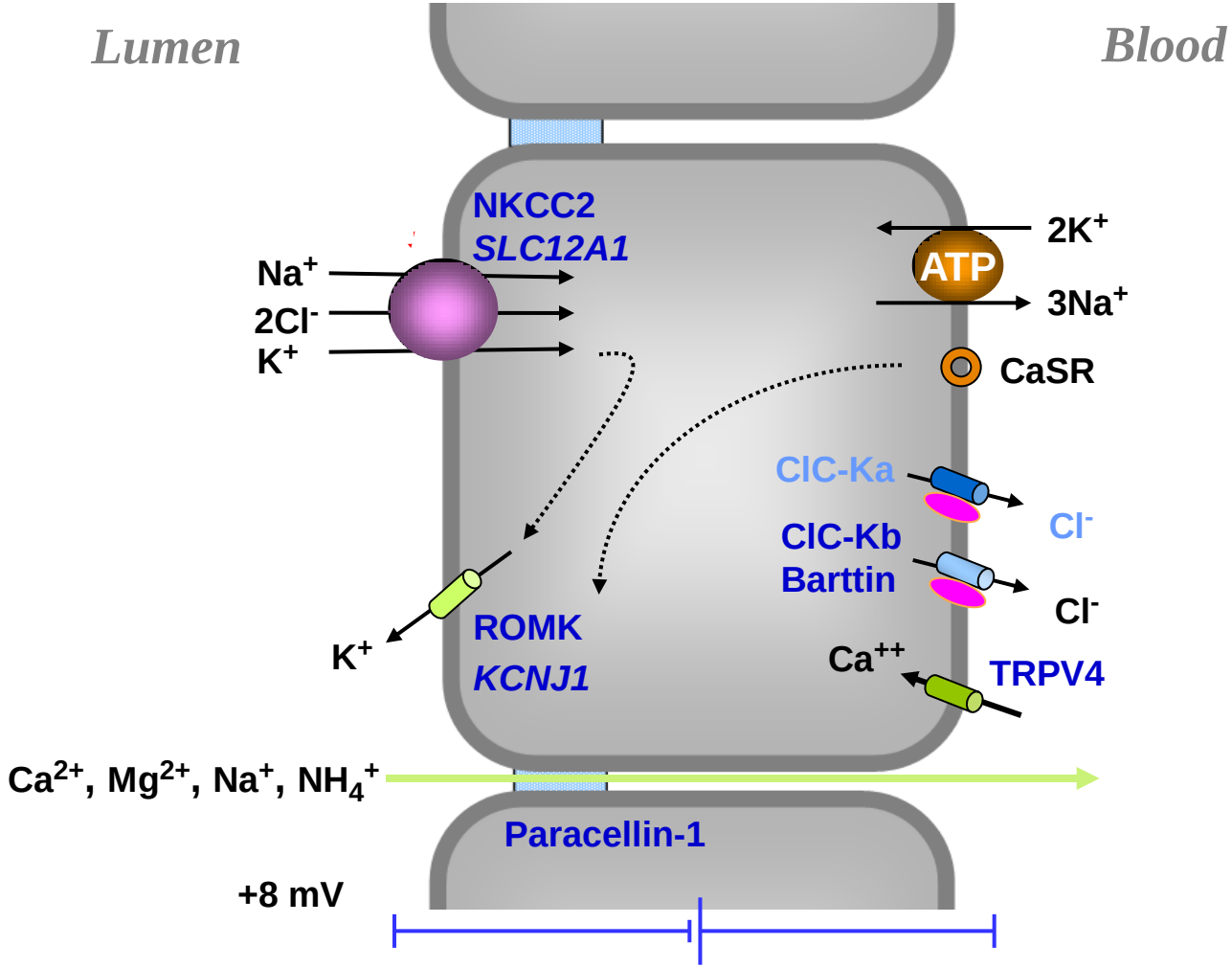
- Serum creatinine 0.5 mg/dl.
- pH 7.56, HCO3 37 mg/dL.
- Serum Na 138 mEq/L.
- Serum K 2.2 mEq/L.
- Serum Cl 93 mEq/L.
- Urinary Chloride 30 mEq/L.

So….

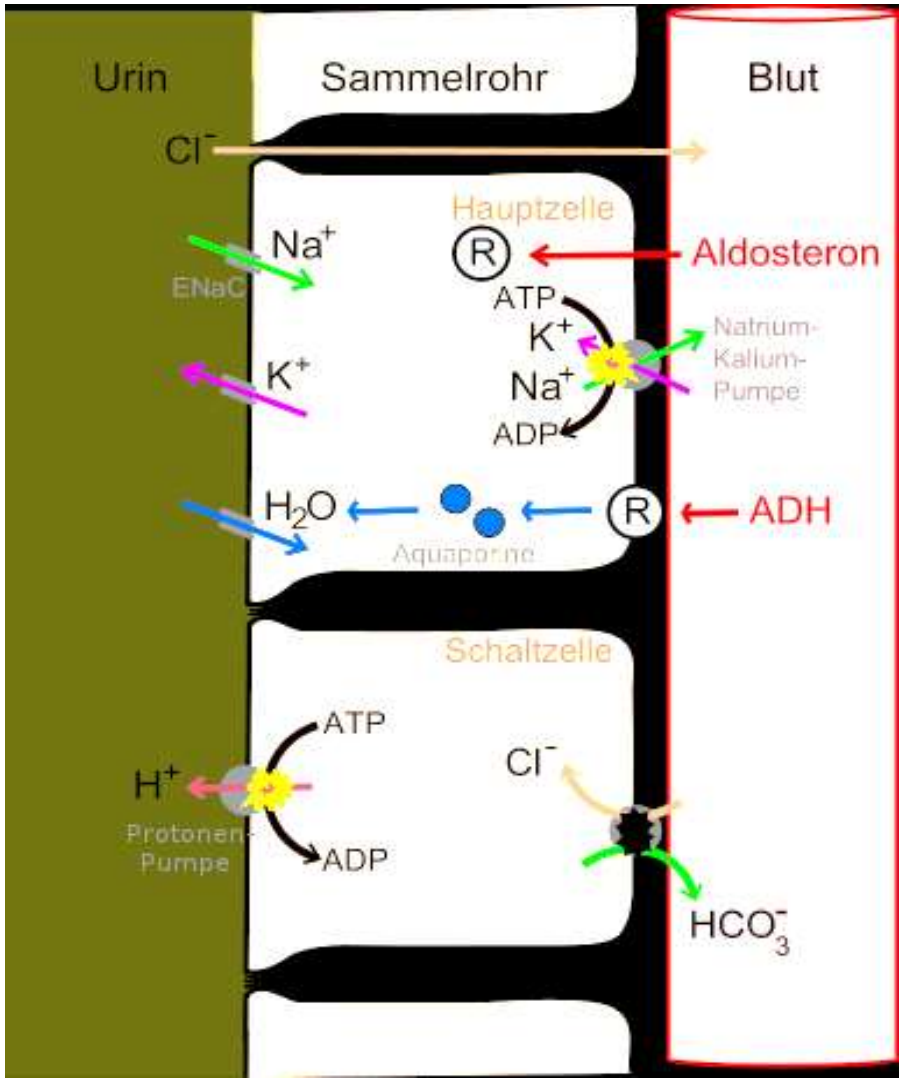
The main abnormality is "hypokalemic metabolic alkalosis with ↑ urine chloride".

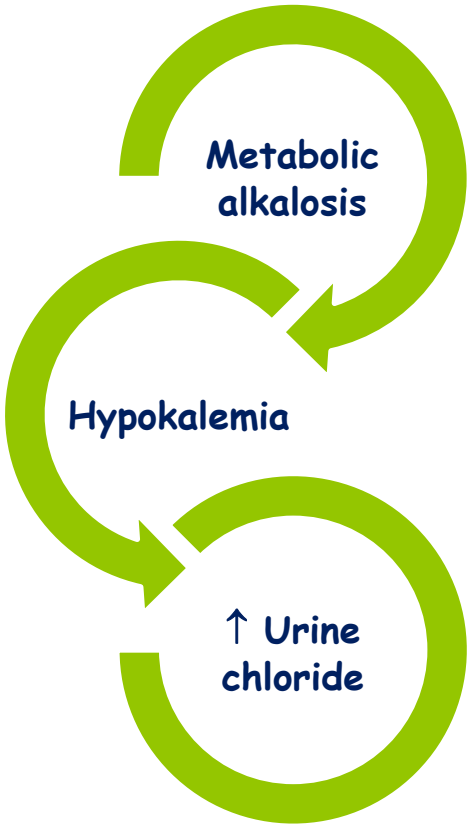

Metabolic alkalosis
Hypokalemia
↑ Urine chloride

Thick ascending limb, Loop of Henle

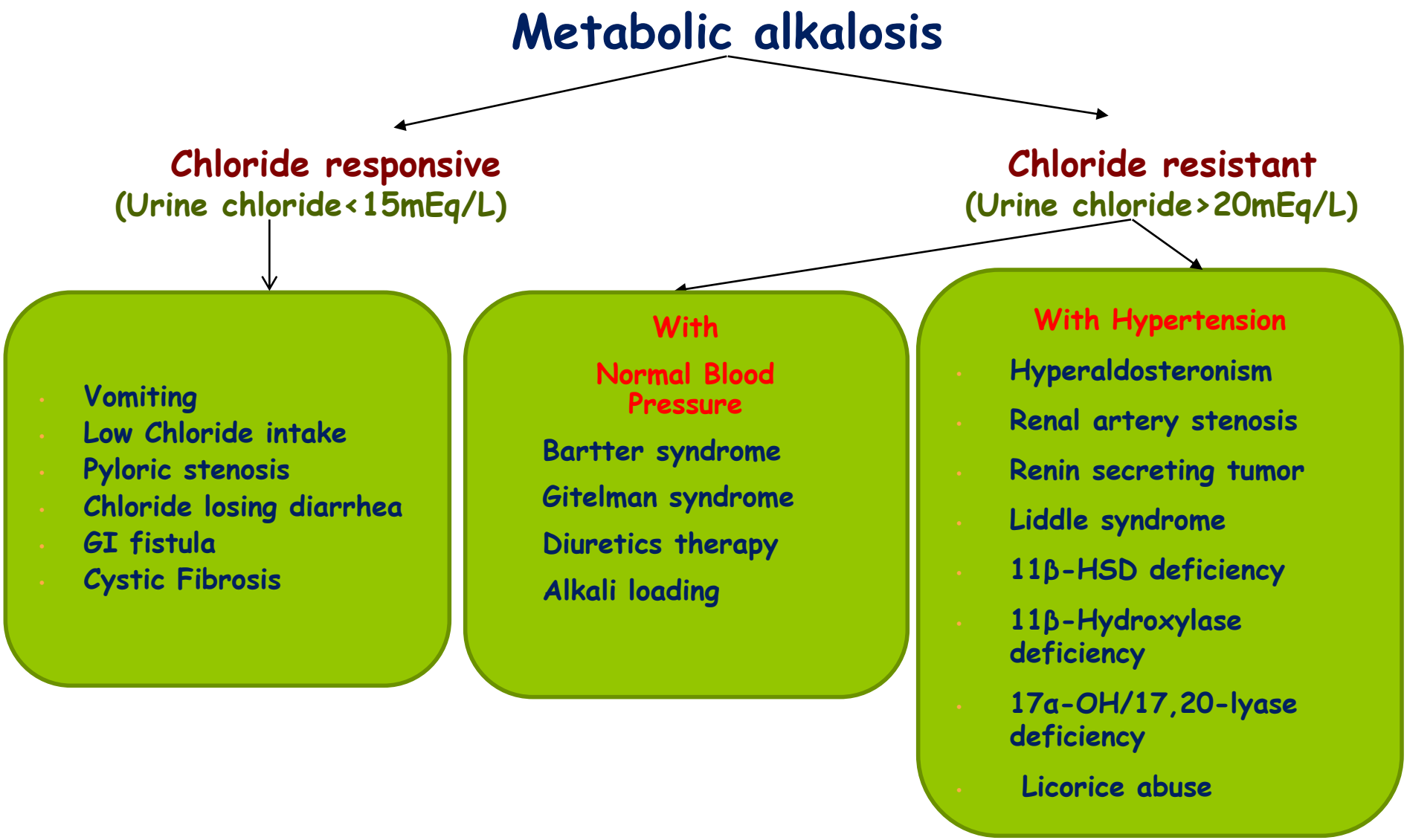


Distal convoluted tubule





Classification of Metabolic Alkalosis



What is the most likely diagnosis?

Back to Our Patient

Urinary Chloride 30 mEq/L

Metabolic alkalosis

Chloride responsive
(Urine chloride<15mEq/L)

- [illegible]
- [illegible]ke
- Pyl[illegible]
- Chl[illegible]diarrhea
- G[illegible]
- [illegible]

Chloride resistant
(Urine chloride>20mEq/L)

With
Normal Blood Pressure

- Bartter syndrome
- Gitelman syndrome
- Diuretics therapy
- Alkali loading

With Hypertension

- Hyperaldosteronism
- Renal artery stenosis
- Renin secreting tumor
- Liddle syndrome
- 11β-HSD deficiency
- 11β-Hydroxylase deficiency
- 17α-OH/17,20-lyase deficiency
- Licorice abuse

Chloride Resistant Metabolic Alkalosis

Normal Blood Pressure

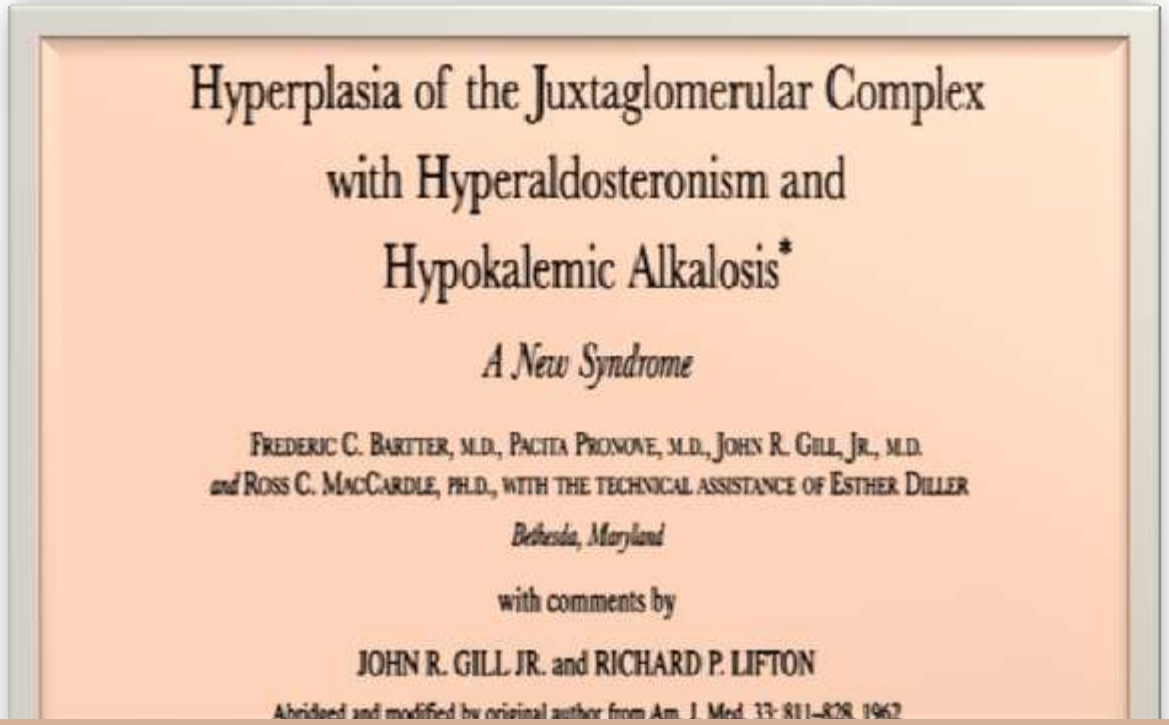
Metabolic alkalosis

Chloride responsive
(Urine chloride<15mEq/L)

Chloride resistant
Urine chloride>20mEq/L

With
Normal Blood Pressure
- Bartter syndrome
- Gitelman syndrome
- Diuretics therapy
- Alkali loading

With Hypertension
- Licorice abuse



Hyperplasia of the Juxtaglomerular Complex with Hyperaldosteronism and Hypokalemic Alkalosis*

A New Syndrome

FREDERIC C. BARTTER, M.D., PACITA PRONOVE, M.D., JOHN R. GILL, JR., M.D. and ROSS C. MACCARDLE, PH.D., WITH THE TECHNICAL ASSISTANCE OF ESTHER DILLER

Bethesda, Maryland

with comments by

JOHN R. GILL JR. and RICHARD P. LIFTON

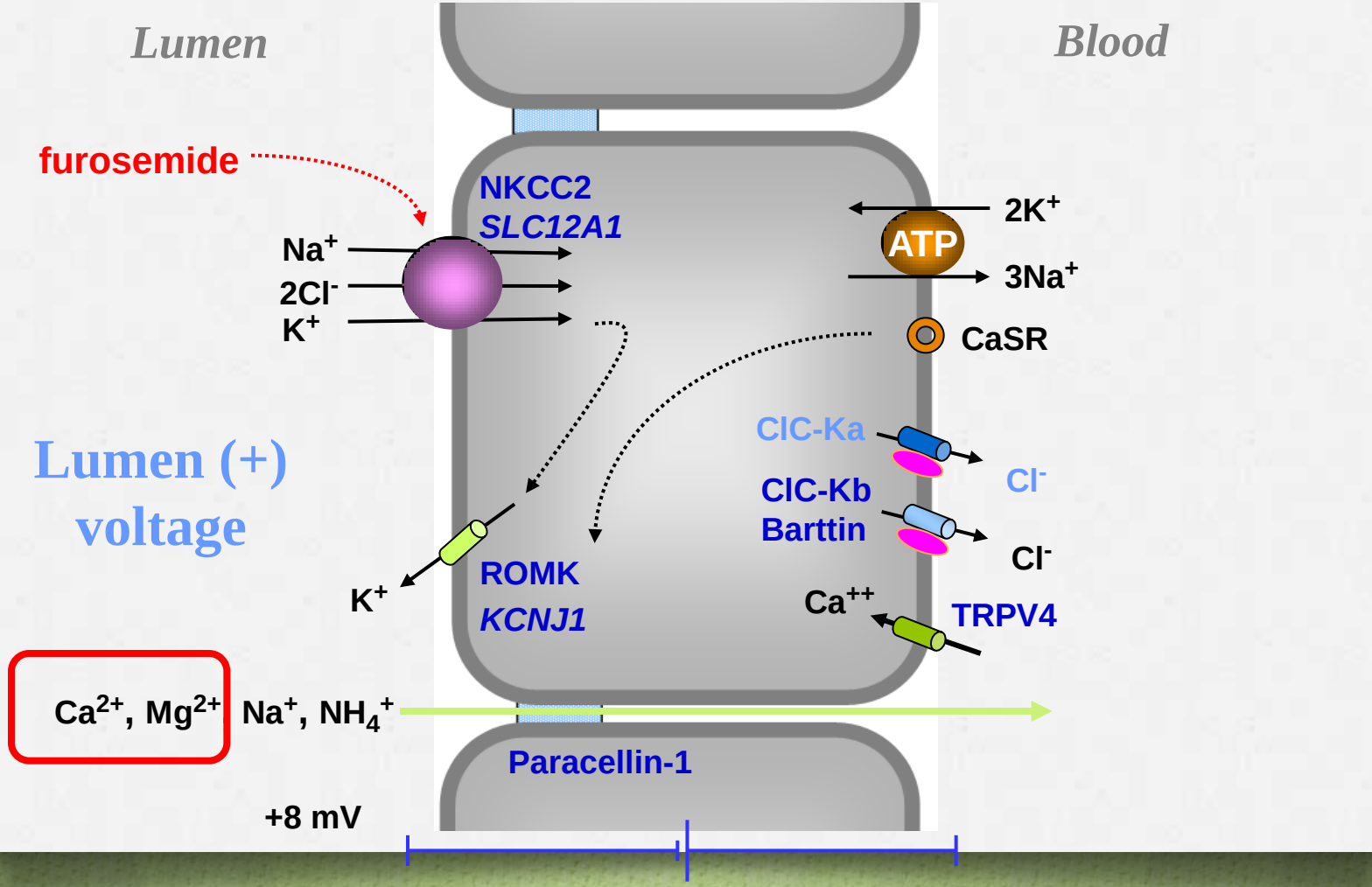
Abridged and modified by original author from Am. J. Med. 33: 811–828, 1962

Classification

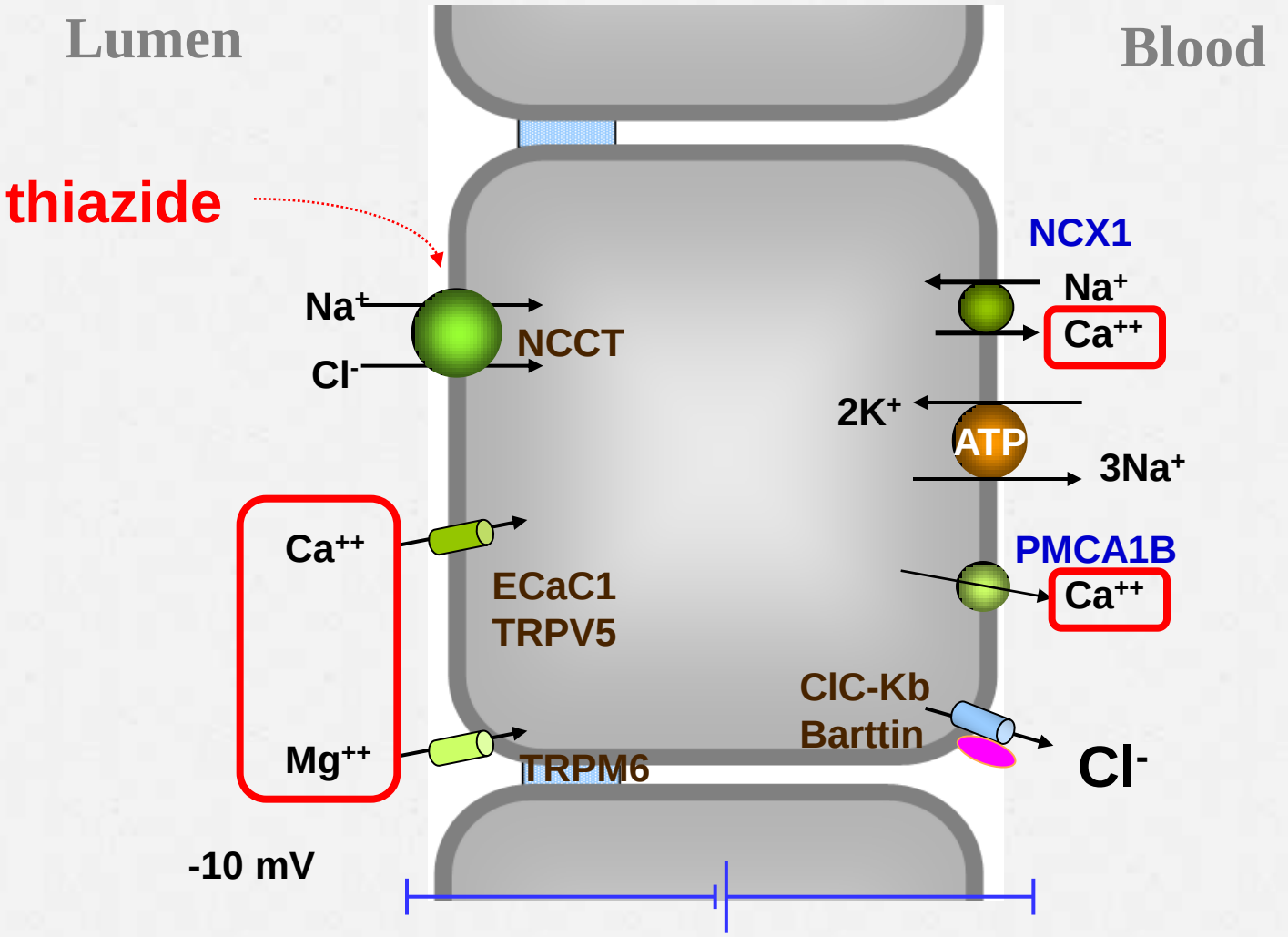
- Neonatal Bartter syndrome.
- Classic Bartter syndrome.
- Gitelman syndrome.


WAKE
UP!

Thick ascending limb, Loop of Henle

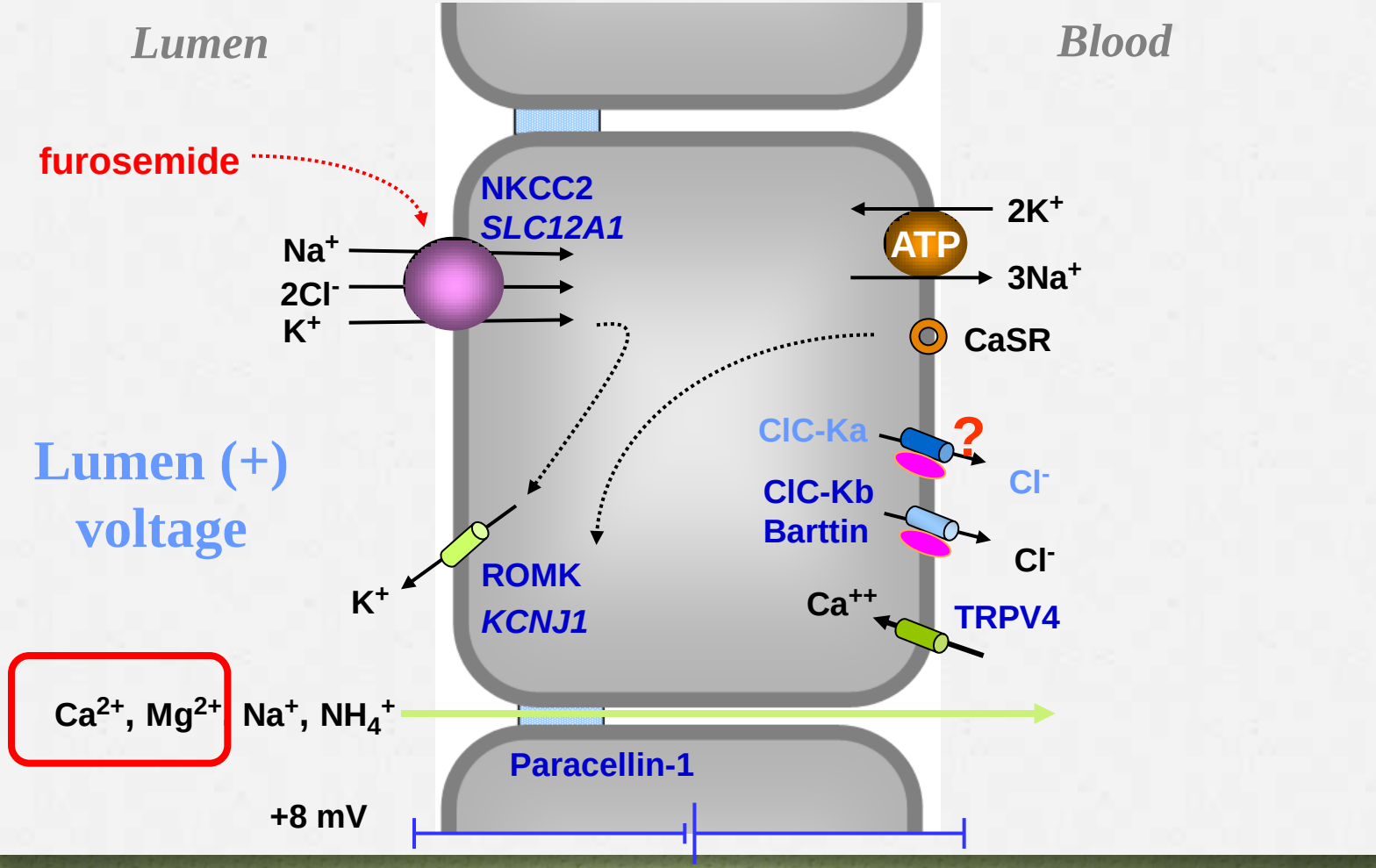


Distal convoluted tubule

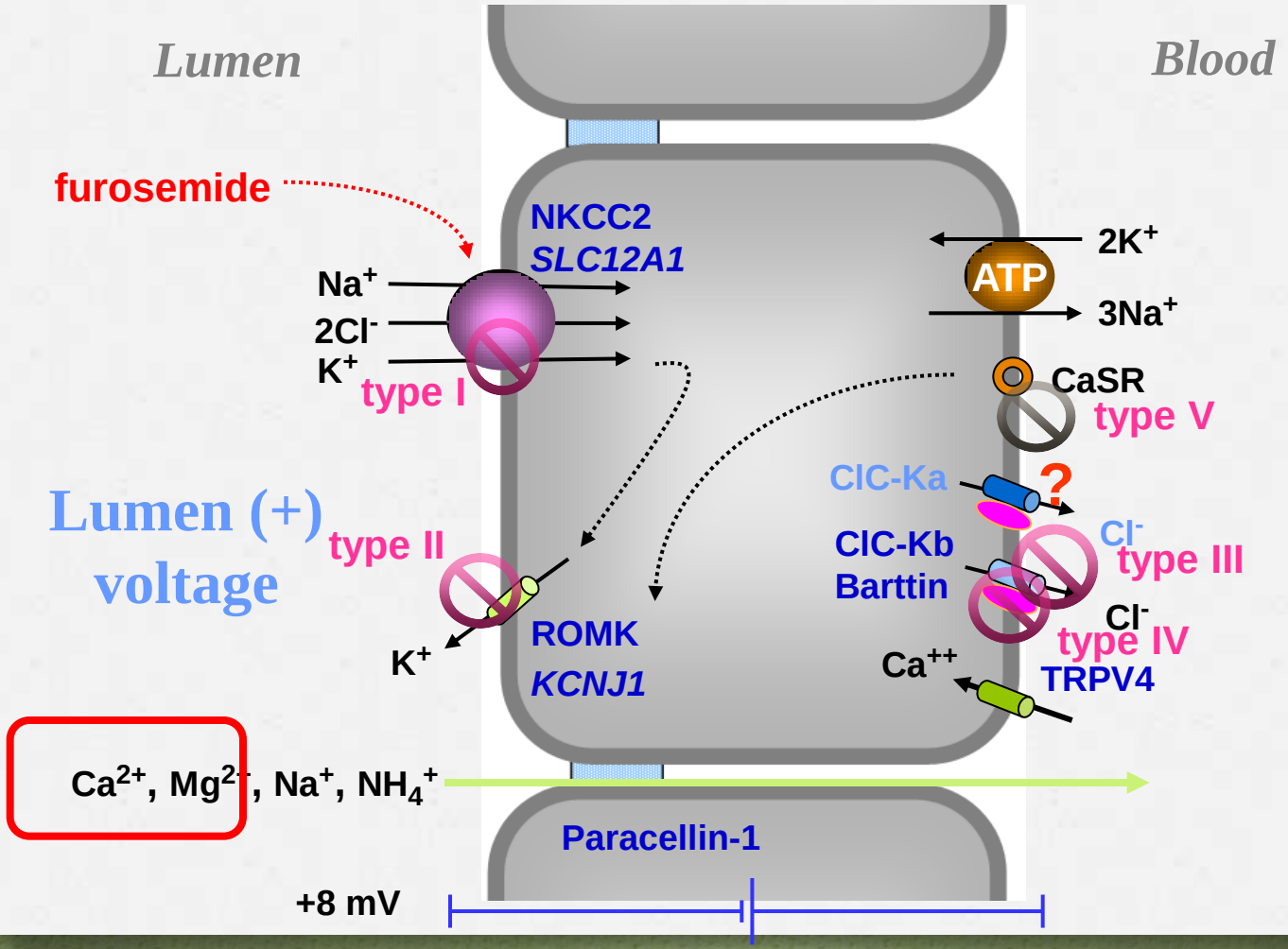


Pathophysiology

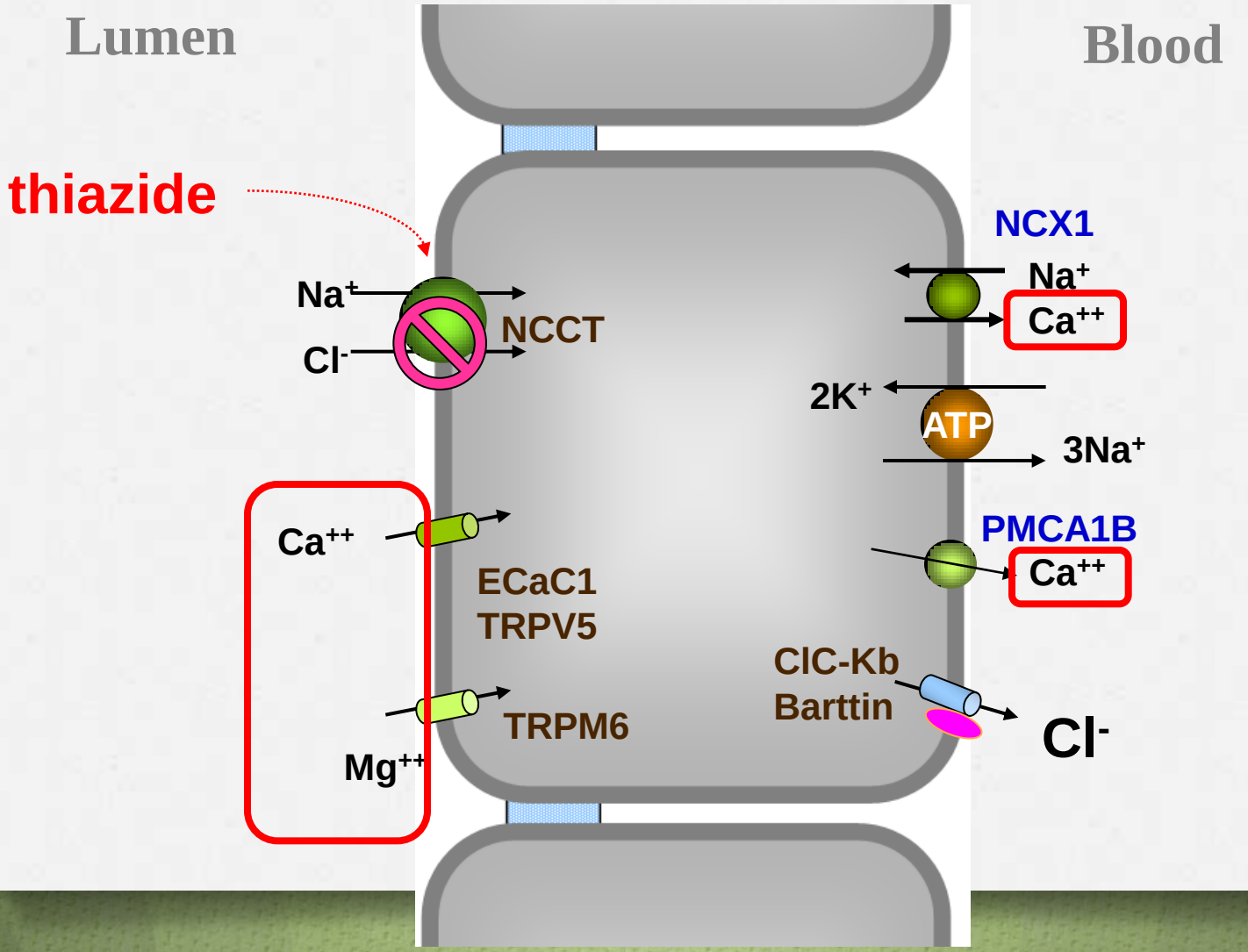
Thick ascending limb, Loop of Henle



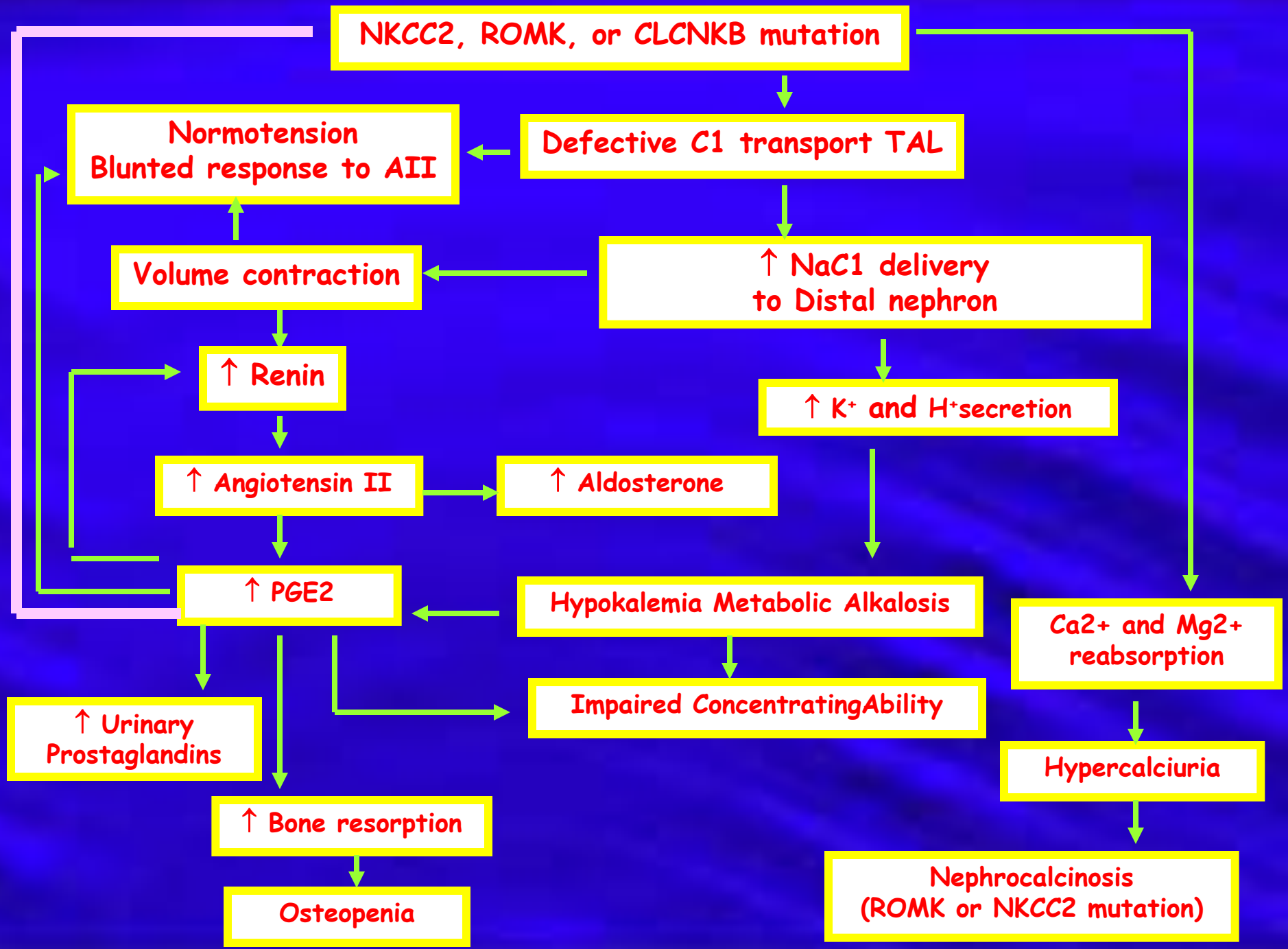
Bartter syndrome



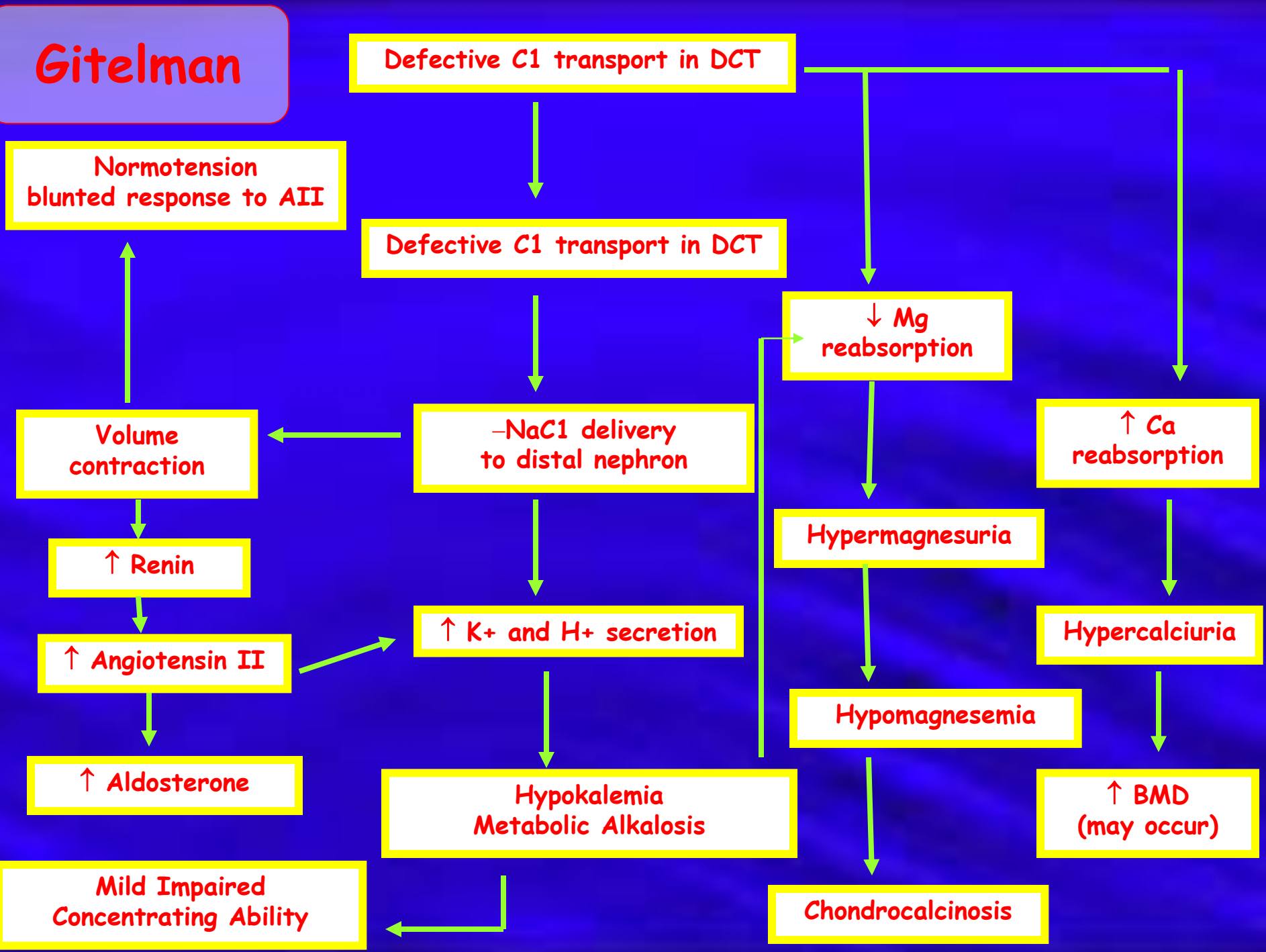
Gitelman syndrome



Bartter Syndrome Genotype-Phenotype Correlations		
Genetic Type	Defective Gene	Clinical Type
Bartter type I	NKCC2	Neonatal
Bartter type II	ROMK	Neonatal
Bartter type III	CLCNKB	Classic
Bartter type IV	BSND	Neonatal with deafness
Bartter type V	CLCNKB and CLCNKA	Neonatal with deafness
Gitelman syndrome	NCCT	Gitelman syndrome


NKCC2, ROMK, or CLCNKB mutation
Defective C1 transport TAL
Normotension
Blunted response to AII
↑ NaC1 delivery
to Distal nephron
Volume contraction
↑ Renin
↑ K+ and H+secretion
↑ Angiotensin II
↑ Aldosterone
↑ PGE2
Hypokalemia Metabolic Alkalosis
Ca2+ and Mg2+
reabsorption
↑ Urinary
Prostaglandins
Impaired ConcentratingAbility
Hypercalciuria
↑ Bone resorption
Osteopenia
Nephrocalcinosis
(ROMK or NKCC2 mutation)

Gitelman


Defective C1 transport in DCT
Defective C1 transport in DCT
Normotension
blunted response to AII
Volume
contraction
↑ Renin
↑ Angiotensin II
↑ Aldosterone
–NaC1 delivery
to distal nephron
↑ K+ and H+ secretion
Hypokalemia
Metabolic Alkalosis
Mild Impaired
Concentrating Ability
↓ Mg
reabsorption
Hypermagnesuria
Hypomagnesemia
Chondrocalcinosis
↑ Ca
reabsorption
Hypercalciuria
↑ BMD
(may occur)


Sum Up!

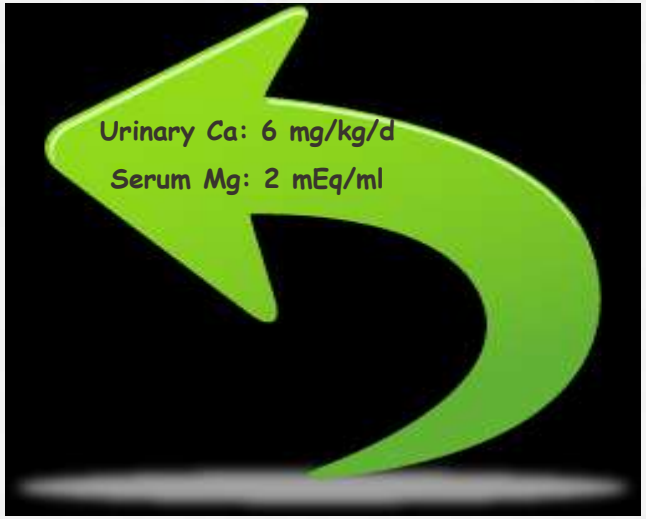
Clinical picture ….

	BS Type I	BS Type III	GS
• Age at presentation	Neonatal	≤ 2 years old	Above 5 years
• Growth retardation	Severe	Mild-moderate	Absent or mild
• Polyuria	Present	Present	May be present
• Nephrocalcinosis	Present	+/-	Absent
• Polyhydramnios	Present	May be present	Absent
• Chondrocalcinosis	Absent	Absent	May be present
• Carpal pedal spasm	Absent	Absent	May be present
• SN Hearing Loss	May be present	Absent	Absent

Biochemical markers ….

	BS Type I	BS Type III	GS
• Hypokalemia	Present	Present	Present
• Metabolic alkalosis	Present	Present	Present
• Hyperreninemia	Present	Present	Present
• Hyperaldosteronemia	Present	Present	Present
• Urinary calcium	Very High	High	Low
• Hypomagnesemia	Absent or mild	Absent or mild	Present
• Urinary prostaglandins	High	High	Normal

Back to Our Patient



Neo[illegible]tter [illegible]

Classic Bartter Syndrome

[illegible]

Clin Nephrol. 2014 Feb;81(2):146-50. doi: 10.5414/CN107606.

Hypokalemic paralysis in a middle-aged female with classic Bartter syndrome.

Chiang WF, Lin SH, Chan JS, Lin SH.

Abstract

Inherited classic Bartter syndrome (cBS) is an autosomal recessive renal tubular disorder resulting from inactivating mutations in the asolateral chloride channel (ClC-Kb) and usually presents in early infancy or childhood with mild to moderate hypokalemia. Profound hypokalemic paralysis in patients with cBS is extremely rare, especially in middle age. A 45-year-old Chinese female patient was referred for evaluation of chronic severe hypokalemia despite regular K+ supplementation (1 mmol/kg/d). She had had two episodes of muscle paralysis due to severe hypokalemia (K+ 1.9 - 2.1 mmol/l) in the past 3 years. She denied vomiting, diarrhea, or the use of laxatives or diuretics. Her blood pressure was normal. Biochemical studies showed hypokalemia (K+ 2.5 mmol/l) with renal potassium wasting, metabolic alkalosis (HCO3- 32 mmol/l), normomagnesemia (Mg2+ 0.8 mmol/l), hypercalciuria (calcium to creatinine ratio 0.5 mmol/mmol; normal < 0.22 mmol/mol), high plasma renin activity, but normal plasma aldosterone concentration. Abdominal sonography revealed neither renal stones nor nephrocalcinosis. Acquired causes of cBS such as autoimmune disease and drugs were all excluded. Molecular analysis of the CLCNKB gene, encoding ClC-Kb, and SLC12A3, encoding the thiazide-sensitive sodium chloride cotransporter (NCC), revealed compound heterozygous mutations in CLCNKB (L335P and G470E) inherited from her parents; her SLC12A3 was normal. These two mutations were not identified in 100 healthy subjects. Her plasma K+ concentration rose to 3 - 3.5 mmol/l after the addition of spironolactone. Inherited cBS may present with hypokalemic paralysis and should be considered in adult patients with hypokalemia and metabolic alkalosis.

Sabina Gallati, PhD
Division of Human Genetics
Department of Pediatrics
University of Bern
Bern, Switzerland
Joachim Weis, MD
Division of Neuropathology
Institute of Pathology
University of Bern
Bern, Switzerland
Stephan Krähenbühl, MD
Division of Clinical Pharmacology and Toxicology
University Hospital
Basel, Switzerland
Jean-Marc Burgunder, MD
Department of Neurology
University of Bern, Inselspital
Bern, Switzerland

Received January 14, 2005. Received revised February 22, 2005. Accepted for publication April 15, 2005.

Address correspondence to Dr Gian Paolo Ramelli, Department of Pediatrics, Ospedale San Giovanni, CH-6500 Bellinzona, Switzerland. Tel: ++41 91 811 9195; fax: ++41 91 811 8787; e-mail: gianpaolo.ramelli@eoc.ch.

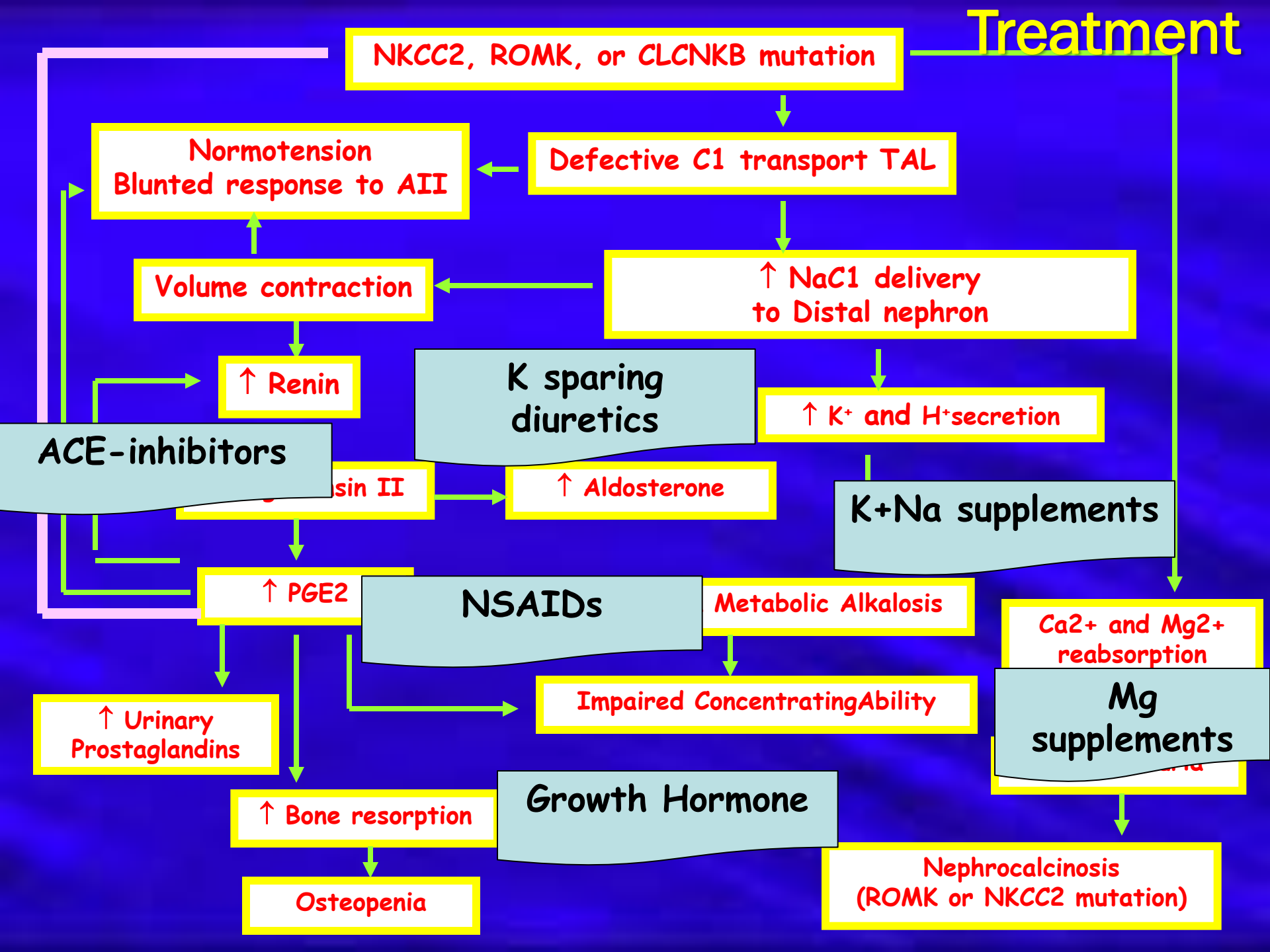
References

1. Goto YI, Matsuoka T, Horai S: A mutation in the tRNA$^{Leu(UUR)}$ gene asso-
ciated with the MELAS subgroup of mitochondrial encephalomyopathies

Case of Bartter Syndrome Presenting With Hypokalemic Periodic Paralysis

ABSTRACT

Hypokalemic periodic paralysis can occur secondarily to excessive potassium loss. Thyrotoxicosis, diuretic ingestions, hyperaldosteronism, barium poisoning, Gitelman syndrome, and Bartter syndrome are among the disorders causing secondary hypokalemic periodic paralysis. Clinical presentation of Bartter syndrome with hypokalemic periodic paralysis is rare. A 12-year-old boy was admitted to our hospital because of transient paralysis. He had been suffering from transient weakness attacks for 2 years and had had a total of 10 attacks, lasting 1 to 3 days. He had growth retardation, polyuria, and polydipsia. Laboratory examinations revealed hypokalemic alkalosis, normomagnesemia, hypercalciuria, and hyperaldosteronism. The clinical and laboratory findings were in accordance with Bartter syndrome. He has been followed up for 6 months and has suffered no further paralytic attacks under indomethacin therapy. This case highlights the importance of blood pH measurement in patients with hypokalemic periodic paralysis: it might prevent misdiagnosis and mismanagement in such diseases. (*J Child Neurol* 2006;21:255–256; DOI 10.2310/7010.2006.00049).


Treatment
NKCC2, ROMK, or CLCNKB mutation
Normotension
Blunted response to AII
Defective C1 transport TAL
Volume contraction
↑ NaC1 delivery
to Distal nephron
↑ Renin
K sparing
diuretics
↑ K+ and H+secretion
ACE-inhibitors
sin II
↑ Aldosterone
K+Na supplements
↑ PGE2
NSAIDs
Metabolic Alkalosis
Ca2+ and Mg2+
reabsorption
↑ Urinary
Prostaglandins
Impaired ConcentratingAbility
Mg
supplements
↑ Bone resorption
Growth Hormone
Osteopenia
Nephrocalcinosis
(ROMK or NKCC2 mutation)


Sum Up!

Hypokalemic metabolic alkalosis

- Hypokalemic metabolic alkalosis is not an uncommon disorder among children.
- Patients are often asymptomatic but they may develop serious neurologic or respiratory symptoms.

- Do not forget to exclude hypokalemic metabolic alkalosis on dealing with a case of unexplained paresis or paralysis.

- The golden point during dealing with hypokalemia is not giving K supplementation, but knowing the cause to treat it.


many
Thanks!